Regulatory Proposal PRO2007-02

Guidelines for the Registration of Low-Risk Biochemicals and Other Non-Conventional Pesticides

This Regulatory Proposal outlines the requirements being proposed by Health Canada's Pest Management Regulatory Agency (PMRA) for registering low-risk biochemicals and other non-conventional pesticides.

This proposal is being distributed for information and comment. Please review this document and provide your written comments within 60 days of the date of publication of this Regulatory Proposal to Publications.

(publié aussi en français)

1 October 2007

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6605C
Ottawa, Ontario
K1A 0K9

Internet: pmra_publications@hc-sc.gc.ca
www.pmra-arla.gc.ca
Facsimile: 613-736-3758
Information Service:
1-800-267-6315 or 613-736-3799
pmra_infoserv@hc-sc.gc.ca

Canada

ISBN: 978-0-662-46885-1 (978-0-662-46886-8)
Catalogue number: H113-8/2007-2E (H113-8/2007-2E-PDF)

Table of Contents

1.0 Introduction

These guidelines outline the scientific and technical information requirements for registering low-risk biochemicals and other non-conventional pesticides. The organization of the information parallels that for other pest control products but, because this particular category is for low-risk pesticides and is very broad, not all information requirements may be appropriate for a specific pesticide. The PMRA recognizes that the information needed to make a regulatory decision should be commensurate with the level of anticipated risks. Therefore, the PMRA is proposing a tiered approach to information requirements for low-risk biochemicals and other non-conventional pesticides. In this, the need for higher-tier information will be determined based on the results from lower tier information and the proposed use pattern.

Although these guidelines are for the registration of low-risk pesticides, the experience of the PMRA is that other regulatory approaches may also be appropriate. The PMRA will consider placing individual, or groups of, low-risk biochemicals and other non-conventional pesticides on Schedule II of the *Pest Control Products Act.* This would exempt these pest control products from registration as long as the products comply with the prescribed conditions laid out in the Schedule. Products would be added to the Schedule when the PMRA has determined that the risks to health and the environment are acceptable, the pesticide has value and scheduling is an efficient regulatory option to facilitate access of these products to the users.

The category low-risk biochemicals and other non-conventional pesticides is broad and includes biochemicals such as natural plant and insect regulators, naturally occurring repellents and attractants, and enzymes. The Organisation for Economic Co-operation and Development has recognized that pheromones, a certain type of biochemical pesticide, warrant a separate unique set of reduced information requirements. The PMRA's information requirements for these are contained in Regulatory Proposal PRO2002-02, *Guidelines for the Research and Registration of Pest Control Products Containing Pheromones and Other Semiochemicals*. **This regulatory proposal on low-risk pesticides is not meant to replace that guidance, but rather to provide guidance for the registration of other low-risk biochemical and non-conventional pesticides for which there are no existing directives or proposals.** When this proposal is finalized, it will be combined with that for pheromones and semiochemicals so that one regulatory directive addresses all types of low-risk biochemical pesticides. Other low-risk pesticides that are included in this proposal in addition to biochemicals are certain other natural substances, certain commodity chemicals and certain devices.

During the development of this regulatory approach, some stakeholders indicated a need for the clarification of the terms "low-risk" and "reduced-risk" (DIR2002-02). In general, reduced-risk status is granted if the characteristics and use of a product are such that the risk to human health or the environment is reduced when compared to alternatives. Reduced-risk status does not necessarily mean reduced information requirements, but does have an expedited review time. Low-risk biochemicals and non-conventional pesticides are a subset of reduced-risk products and may involve both reduced information requirements and an expedited review time.

This regulatory proposal has been developed in response to the requirement of the *Pest Control Products Act* to "expedite evaluations with respect to a pest control product that may reasonably be expected to pose lower health or environmental risks" [Section 7(3)]. In developing these proposed guidelines, the PMRA sought the advice of its Pest Management Advisory Council, and the guidelines presented here are consistent with their recommendations. In addition, the PMRA considered the regulatory requirements of other countries, particularly those of the United States Environmental Protection Agency (USEPA) to further harmonize regulatory approaches. Also, the PMRA considered the demand for lower risk pesticides from the organic pest management sector and residential domestic class markets as well as concern over the use of certain commodity chemicals with known pesticidal properties in Canada that are not registered as pesticides and are without the necessary safety information and use directions for use as pesticides.

2.0 Categories of Low-Risk Biochemicals and Other Non-Conventional Pesticides

2.1 Biochemicals

A biochemical pesticide is a category of biopesticide that:

- is a naturally-occurring substance or its synthetic analogue that is functionally identical to the naturally-occurring substance;
- has a history of equivalent exposure to humans and the environment demonstrating minimal toxicity or in the case of a synthetically derived biochemical pesticide, is equivalent to a naturally-occurring substance that has such a history; and
- has a non-toxic mode of action to the target pest(s) including, but not limited to, attraction, repulsion, growth regulation, induction of systemic acquired resistance, and physical modes of action.

Biochemical pesticides include, but are not limited to, semiochemicals (pheromones and kairomones), natural plant and insect regulators, naturally occurring repellents and attractants, and enzymes. The synthetic analogue of a naturally occurring substance is included as a biochemical because it is recognized that it may often be more economically feasible to produce the biochemical synthetically; however, the synthetic analogue must be functionally identical to the naturally occurring substance.

The PMRA recognizes that while many biochemical pesticides pose a low risk, other plant-derived pesticides, such as nicotine, can be quite toxic. A naturally occurring pesticide which is inherently toxic would not be considered under the low-risk pesticide scheme, but rather the information requirements would be that of a conventional pesticide to allow the PMRA to adequately assess the risks. The non-toxic mode of action criterion for biochemicals would exclude naturally occurring pesticides such as pyrethrins from the low risk scheme as they are directly toxic to certain insects.

The definition above is equivalent to that proposed by the USEPA Proposed Rule published in the Federal Register in March 2006 (40 CFR Part 158L). As stated in the introduction, the PMRA already has a regulatory proposal for the regulation of pheromones and semiochemicals and for the procedure for joint review of semiochemicals with the USEPA (PRO2002-02). **This regulatory proposal is not meant to replace that guidance but to provide guidance for the registration of other low risk biochemicals and non conventional pesticides for which there are no existing directives or proposals.** When this proposal is finalized, it will be combined with that of the pheromones and semiochemicals so all categories of low-risk biochemical pesticides are in one set of guidelines.

The PMRA may review, on a case-by-case basis, naturally-occurring pesticides that do not clearly meet the definition of a biochemical pesticide in an effort to ensure, to the greatest extent possible, that only the minimum testing sufficient to make scientifically sound regulatory decisions would be conducted. The PMRA will review applications for registration of naturally-occurring pesticides to determine whether to review the pesticide under the low-risk scheme.

2.2 Non-Conventional Pesticides

The PMRA is proposing to consider the following categories of non-conventional pesticides eligible for review under the low-risk pesticide scheme if it is demonstrated that they are of low risk.

2.2.1 Substances That Are Naturally Present or Derived by Simple Processing

This could include food stuff (commonly consumed food items), feedstuffs, animal products derived by simple processing, certain mechanically processed natural minerals and non-food plant parts.

2.2.2 Certain Types of Plant Extracts and Essential Oils

Certain mechanically processed plant extracts are eligible for review under this stream. Essential oils are volatile oils that give distinctive odour or flavour to a plant, flower or fruit. Not all essential oils are eligible for review under this stream. For essential oils and plant extracts, a case-by-case approach will be taken based on the processing method, characterization of components, toxicity and use pattern (exposure).

2.2.3 Certain Commodity Chemicals

These chemicals are widely available in society and often have a range of uses that are non-pesticidal. They are generally not directly marketed for their pesticidal properties, but they may have minor pesticidal uses. These substances could be food grade or non-food grade and are generally processed or refined substances.

2.2.4 Certain Devices

A device is any instrument or contrivance intended for trapping, destroying, repelling or mitigating any pest. The proposed regulatory approaches for devices will be consistent with Schedules I and II of the Pest Control Products Regulations.

As some of the above categories of pesticides (2.2.1–2.2.4) are not in purified/refined form, it is important to prevent the unintentional introduction of other toxic substances from the proposed use (e.g. mycotoxins, heavy metals, etc.). The Agency also recognizes that some of the products from the above groups may not be of low risk because of high toxicity and/or exposure and thus require detailed assessment of risk. Therefore, a reduced timeline and a reduced information set would not be appropriate. Further detail on information requirements is provided in Section 4.0.

3.0 Characteristics of Low-Risk Pesticides

Pesticides for consideration under this proposed registration scheme have some or all of the following characteristics.

- Low inherent toxicity to non-target organisms

  Products with low inherent toxicity to humans and other non-target organisms are expected to have minimal anticipated environmental and health risks even when exposure is extensive. It should be pointed out that substances with chronic toxicity, carcinogenicity, mutagenicity, neurotoxicity and reproductive/developmental effects are not eligible for review under this low-risk scheme.

- Not persistent in the environment when environmental exposure is expected

  The PMRA recognizes that certain naturally occurring substances are relatively persistent in the environment; therefore, a case-by case approach will be taken to assess this characteristic when determining if a pesticide poses low risk.

- Used in such a manner as to not result in significant exposure

- Widely available to the public for other uses and has a long history of equivalent exposure to humans and the environment with minimal toxicity (the level of exposure should be similar to the proposed uses)

- Non-toxic mode of action (i.e. pesticidal action is not the result of target organism toxification)

  The phrase "non-toxic mode of action" is interpreted to include such pest control mechanisms as attraction, repellency (including irritants), growth regulation/developmental changes and induction of systemic acquired resistance as well as physical modes of action such as desiccation, coatings or smothering, e.g. by naturally occurring oils. The Agency recognizes that physical modes of action, e.g. suffocation, may be lethal to the target pest, but they are considered to be a non-toxic mode of action because they do not involve toxic chemical- or poison-induced effects.

- Unlikely to cause pest resistance

In addition to the above, to be considered in this low-risk pesticide scheme, any formulants used in the end-use product must be on List 4A or 4B. List 4A formulants do not have any restrictions of use. However, List 4B formulants have restrictions or limitations on use that also apply to low-risk pesticides. Applicants should refer to Regulatory Directive DIR2006-02, *Formulants Policy and Implementation Guidance Document*.

Applicants are required to provide scientific evidence as to why their active ingredient and/or end-use product is eligible for review under the low-risk pesticide scheme using the above or additional characteristics (e.g., area of use, conditions of use), as appropriate. It is anticipated that many low-risk products will have available information, either because of approvals in other countries or through other programs or regulatory processes when used in non-pesticidal ways. Applicants can use foreign reviews, published research articles, original study results and/or consult scientists or experts in the public or private sectors in developing the evidence. The PMRA will make its decisions concerning eligibility on a case-by-case basis given the totality of evidence available and the product, its use and type of label claim being made. Further detail on information requirements is provided in Section 4.0.

4.0 Tiered Information Requirements

Prior to making a registration decision, the PMRA conducts assessments to ensure that the pesticide will have value and will not pose unacceptable risks to human health or the environment. To conduct these assessments, the Agency requires that registrants submit a variety of information about the composition, toxicity, transformation, efficacy and other characteristics of the pesticide. The PMRA recognizes that the information needed to make a regulatory decision should be commensurate with the level of anticipated risks. Therefore, the PMRA is proposing a tiered approach to information requirements for low-risk biochemicals and other non-conventional pesticides. In this approach, the need for higher-tier information will be determined based on the results from lower-tier information and the proposed use pattern. Higher-tiered information will be required if the potential for adverse effects is observed in the lower-tier information. The lower-tiered information is a subset of that required for conventional pesticides.

As a wide variety of products could be eligible for review under this scheme, applicants are encouraged to begin by consulting Appendix I for general guidance on information requirements. Each requirement identified in the information requirement tables contained in Appendix I has been assigned a status of "R" or "CR". The "R" designation means that information is required. The requirement may be satisfied by submitting:

- information on the test substance;
- published information (e.g. foreign reviews, published research articles);
- surrogate information or bridging information to another substance, if both substances belong to a well-known group of substances; or
- a rationale to waive the requirement based on sound scientific reasoning or because it may be impractical or unnecessary to address the underlying concern behind the information requirement.

The "CR" designation means that the information is only required under the conditions indicated in the table's test footnote(s). Many of the information requirements marked CR represent types of information that are only required for high exposure scenarios or if hazards are noted from other information requirements.

If needed, the PMRA will help applicants in determining what information is needed to support registration of a low-risk pesticide. Applicants are responsible for providing sufficient information to support a regulatory decision. Applicants, therefore, are strongly encouraged to make use of the presubmission consultation process of the Agency described in Section 5.1 to receive guidance on the information requirements.

It should be noted that, if any information submitted by the applicant or gathered by the Agency during evaluation indicates that the product is not of low risk, additional information may be requested to characterize the risk or the Agency may move the pesticide to the conventional pesticide evaluation scheme. Information requirements will be assessed on a case-by-case basis. Depending on the level of anticipated risk based on toxicity and exposure, a qualitative or quantitative risk and value assessment will be conducted to support a regulatory decision.

4.1 Information Required for Product Chemistry

Information required for product chemistry is the same as that required for conventional pesticides. Information on product analysis is used to determine whether impurities of toxicological or environmental concern are present in the pesticide and formulated products. The applicant must characterize the composition of the technical grade active ingredient. The product specifications must be provided and, if possible, the active ingredient and impurities should be identified. For the end-use product, the specifications must include information on the technical grade active ingredient used, and the formulants must be from List 4A or 4B. Information requirements include product identity and composition information, physical and chemical characteristics, and chemical analysis.

More detailed information on information requirements can be found in Appendix I, Tables 1 and 2.

4.2 Information Required for Assessment of Risk to Human Health

4.2.1 Toxicology Information

The applicant must provide evidence that the technical grade active ingredient is of low acute toxicity (oral, dermal and inhalation) and does not demonstrate any biologically significant short-term or chronic toxicity. They must also demonstrate that the technical grade active ingredient is not genotoxic, mutagenic, a neurotoxicant, a reproductive toxicant, an oncogenic compound, or a prenatal developmental toxicant. Applicants must also show the technical grade active ingredient does metabolize into compounds of toxicological concern or into compounds anticipated to bioaccumulate.

Associated end-use products should be of low acute toxicity (oral, dermal, inhalation), not corrosive to the eyes or skin when used as a domestic class product and not a dermal sensitizer. In addition, these products should not result in an adverse effect to domestic animals if the product's use will result in exposure to pets.

If supporting evidence is not available from the publicly available literature or new studies, the applicant is invited to provide the PMRA with scientifically valid rationales that address all of the toxicological endpoints listed above. Depending on the type of product and use pattern, a long history of equivalent exposure to humans (similar to the level of exposure that would be incurred by the proposed use of the product), e.g. 50 years, may be an acceptable scientific rationale at the presubmission stage or preliminary review phase in the registration process. More detailed information on information requirements can be found in Appendix I, Table 3.

4.2.2 Occupational and Bystander Exposure Information

The applicant must submit a draft label for the technical grade active ingredient and for any associated end-use products as well as provide necessary information as it relates to the anticipated exposure. This can include the following:

- typical work day;
- amount of active ingredient to be handled;
- site, timing and method of application;
- individuals involved;
- mixing/loading method;
- clean-up and repair activities;
- personal protective equipment and clothing during mixing, loading, application and during any postapplication activities;
- crop cultivation practices;
- proposed restricted-entry intervals;
- re-entry activities;

- timing, frequency and duration of any re-entry activities;
- type of field workers;
- the intensity and the degree of contact and which body parts are anticipated to come in contact with treated surfaces.

The applicant is also expected to address the potential for exposure to bystanders, particularly those in nearby residential areas.

More detailed information on information requirements can be found in Appendix I, Table 4.

4.2.3 Dietary Exposure Information

If the end-use product is to be applied on food and/or feed stuff, the applicant should be able to provide evidence that anticipated residues of the parent compounds and any metabolites will not pose a toxicological concern. The applicant may use available information or scientifically valid rationale(s). As with toxicology, a long history of equivalent level of exposure (similar to the level of exposure that would be incurred by the proposed use of the product) to humans, e.g. 50 years, may be an acceptable scientific rationale at the presubmission stage or preliminary review phase in the registration process.

More detailed information can be found in Appendix I, Table 5.

4.3 Information Required for Assessment of Risk to the Environment

The PMRA is proposing a tiered system of environmental effects and fate information to assess the potential risks of pesticides to non-target aquatic and terrestrial organisms (i.e. vertebrates, invertebrates and plants) under conditions of use. The information from lower tiers is used to indicate requirements for higher-tier information. Applicants are encouraged to submit any relevant information (i.e. environmental fate and toxicity) in addition to that required as this will facilitate the evaluation of the pesticide.

In Tier I, the applicant must provide evidence that the technical grade active ingredient is of low acute toxicity to non-target aquatic and terrestrial organisms. The applicant should consider the use pattern when determining the relevant environmental media for exposure (i.e. soil, water, sediment, air); thus, the potential non-target organisms exposed. Lack of exposure and/or high volatility are acceptable scientific rationales to waive some environmental toxicity information requirements.

If Tier I information indicates a potential for adverse effects, Tier II information, including information to characterise the environmental fate of the pesticide is required. Concerning the fate, the applicant must submit information indicating the level of persistence in the environment and the potential for mobility (if applicable, based on the proposed use pattern).

If Tier II environmental fate information and the use pattern indicate a potential for exposure, additional Tier III information will be required to characterize the chronic/subchronic toxicity to non-target organisms.

The above information provides the foundation for the environmental risk assessment and allows the PMRA to determine any appropriate precautionary statements or risk mitigation measures necessary to support registration.

More detailed information can be found in Appendix I, Table 6.

4.4 Information Required for Assessment of Value

In the *Pest Control Products Act* , value of a pest control product means "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's:

- efficacy;
- effect on host organisms in connection with which it is intended to be used; and
- health, safety and environmental benefits and social and economic impact."

The applicant must submit efficacy information consisting of supporting evidence, experimental trials, published studies or scientific rationales to demonstrate the efficacy of the product for the proposed use. This information must support the conclusion that the product produces the effect claimed on the label when used as directed and that the effect can be attributed to the product and not to some other factor.

For most low-risk products, there is not a prescribed or specified number of studies, number of years over which trials must be conducted or a predetermined level of control that must be achieved. In some cases, a limited number of trials, if conducted with reasonable pest pressure under normal crop production or use conditions, may be sufficient to support a use claim. In most cases, establishment of a lowest effective rate will not be required for non-conventional low-risk pesticides.

The PMRA recognizes that some low-risk pesticides may not be as efficacious as an available commercial standard treatment and that label claims may, therefore, be different than those for conventional pesticides. If a low-risk pesticide product is not effective enough to support a standard use claim, a lower level claim such as "reduces damage, reduces annoyance, reduces innoculum, reduces populations, suppresses symptoms or may inhibit" may be acceptable provided that the applicant can show that the demonstrated level of performance has value. Applicants are encouraged to submit any information describing the value of the pesticide as a pest management tool, in addition to its efficacy.

More detailed information can be found in Appendix I, Table 7.

5.0 Submission Process

5.1 Presubmission Consultation

The main objectives of presubmission consultations for low-risk biochemicals and other non-conventional pesticides are to determine:

- whether the proposed product is eligible for review under the PMRA's low-risk pesticide scheme; and
- the information requirements.

Applicants are strongly encouraged to request a presubmission consultation with the Agency, particularly those who are not familiar with the Canadian regulatory system (e.g. first time applicants) or those who need assistance in determining the information requirements. Presence of technical expertise during presubmission discussion is encouraged for better exchange of scientific information.

Applicants should contact the PMRA for information on appropriate contacts for a presubmission consultation. Applicants may contact the PMRA through the following presubmission e-mail address: pmra-arla_presubs@hc-sc.gc.ca. An information package must be submitted at least 45 days prior to the proposed meeting date. As described in Section 3.0 of this document, applicants are required to provide scientific evidence or rationales as to why their product is eligible for review under this low-risk pesticide scheme. The PMRA will then establish, in discussion with the applicant, the information requirements. If it has been determined that the proposed product is not eligible for the low-risk scheme, the applicant will be notified as soon as possible, and the product will be referred to the conventional pesticide review stream.

The applicant must provide a cover letter requesting a presubmission meeting and a proposed agenda of the issues to be discussed as well as the following minimum information package:

- a draft label outlining the proposed performance claims, directions for use, crops or use sites, target pests, application rates;
- a completed Statement of Product Specification Form;
- brief description of manufacturing information;
- rationale and supporting evidence (with proper reference) for consideration to the low-risk pesticide scheme—information or rationales supporting the considerations (as applicable) as outlined in Sections 3.0 and 4.0 of this document must be submitted; the PMRA will consider published, scientifically valid evidence from acceptable foreign regulatory reviews, published research articles or original study results.
- international regulatory status, if applicable; and
- other relevant information, e.g. depending on the development stage of the proposed product, short summaries of other available evidence on the health and environmental risks and value should also be submitted.

Subsequent to a presubmission consultation, the information requirements for the specified product(s) and use pattern will be communicated to the applicant. A copy of this communication must be enclosed with the submission for registration.

5.2 Submission of Information for Regulatory Decision Making

Only complete submissions will be considered for review by the Agency. Details on how to prepare a submission package can be found in Regulatory Directive DIR2006-05, *Requirements for Submitting Data Index, Documents and Forms*.

All information requirements identified during the presubmission consultation must be addressed using appropriate information from scientifically valid sources (e.g. peer reviewed scientific journals, acceptable foreign reviews etc.), new studies or requests for waivers using scientific rationales. The PMRA will accept any existing scientifically valid information already available from the public domain that are relevant to make a risk or value determination of low-risk products for the proposed use.

If the applicant did not make use of the presubmission consultation process to determine whether the proposed product meets the low-risk scheme or to identify the information requirements, the PMRA will assess the rationale submitted by the applicant in support of the low-risk scheme during the review process. The Agency will also use submitted information on the inherent toxicity of the pesticide along with its use pattern, efficacy and product characterization as the basis for deciding if additional information is needed to support its use.

If there is insufficient information for the PMRA to determine whether the substance is eligible for review under this low-risk pesticide scheme or to do a value or risk assessment, the PMRA will notify the applicant of the additional information requirements.

5.3 Performance Standards and Fees

The performance standard for submission review of low-risk pesticides will be similar to that of the USEPA, with review times of 12–15 months for new active ingredients and end-use products, depending on the use pattern. Joint reviews and workshares of low-risk pesticides with other countries will be considered, and it is anticipated that in those cases timelines will be shortened.

Some of the low-risk products will be eligible for fee exemption or reduced fee status as described in the PMRA's *Guidance Document on Pest Control Product Cost Recovery Fees*. If the pest control product fee regulations are revised, the PMRA will explore the possibility of lower fees for low-risk pesticides to facilitate access to these products.

6.0 Regulatory Options for Low-Risk Pesticides

Pesticides are subject to the *Pest Control Products Act* and Regulations. It is anticipated that registration will continue to be the route most commonly used for low-risk pesticides.

Schedule II of the Pest Control Product Regulations exempts a variety of types of products from registration as long as the products comply with the prescribed conditions. In each of those cases, the prescribed conditions identify and address the concerns that would ordinarily be dealt with on a case-by-case basis in the registration process through the imposition of conditions of registration. For example, products on Schedule II include those treated with registered pest control products, swimming pool and spa products that contain registered active ingredients and meet prescribed ingredient concentrations and label conditions, and certain devices that meet prescribed label conditions and Canadian Standards Association standards. The PMRA will consider placing individual, or groups of, low-risk biochemicals and other non-conventional pesticides on Schedule II when it has determined that the risks to health and the environment are acceptable and the pesticide has value, and scheduling is an efficient regulatory option to facilitate access of these products to the users. In the review of certain pest control products to date, scheduling may be the best long term option, but it is anticipated that registration will continue to be the preferred option for the majority of low-risk products.

During the development of these guidelines, the PMRA used an interim approach to regulating certain low-risk pesticides after having determined the risks and value were acceptable. In those cases, the PMRA provided a letter to the applicant stating the product can be used under specific conditions on an interim basis, without the product being registered. An example of where the PMRA has used this approach include traps containing solely pheromones or other semiochemicals as active ingredients primarily used to control household pests in residential areas.

As with conventional pesticides, low-risk pesticides are eligible for exemption from registration for research purposes (DIR98-05) and for the own use import program, subject to compliance with prescribed conditions.

List of Abbreviations

CHO	Chinese hamster ovary
CR	conditionally required
EP	end-use product
HGPRT	hypoxanthine-guanine phosphoriboxyl transferase
ISP	integrated system product
L	litre(s)
mg	milligram(s)
NR	not required
PHED	Pesticide Handlers Exposure Database
PMRA	Pest Management Regulatory Agency
R	required
TGAI	technical grade active ingredient
tk	thymidine kinase
XPRT	xanthine-guanine phosphoriboxyl transferase
USEPA	United States Environmental Protection Agency

Appendix I Information in Support of Registration of Low-Risk Biochemical or Other Non-Conventional Pesticides

Table 1 Chemistry Information Requirements for Technical Grade Active Ingredients

Data Code (DACO)	Information Requirement	Required	Test Notes
0	**Index**	**R**	
1	**Label**	**R**	
2	**Chemistry Requirements for the Registration of a Technical Grade of Active Ingredient (TGAI)**		
2.1	Applicant's Name and Office Address	R	1
2.2	Manufacturer's Name and Office Address and Manufacturing Plant's Name and Address	R	1
2.3	Product Trade Name	R	1
2.3.1	Other Names	R	1
2.4	Common Name	R	1
2.5	Chemical Name	R	1
2.6	Chemical Abstracts Registry Number	R	1
2.7	Structural Formula	R	1
2.8	Molecular Formula	R	1
2.9	Molecular Weight	R	1
2.11	**Manufacturing Methods for the TGAI**		
2.11.1	Manufacturing Summary	R	1
2.11.2	Description of Starting Materials	R	1
2.11.3	Detailed Production Process Description	R	1
2.11.4	Discussion of Formation of Impurities	CR	1, 2
2.12	**Specifications**		
2.12.1	Establishing Certified Limits	R	1
2.12.2	Control Product Specification Form	R	1
2.13	**Preliminary Analysis**		1, 3, 4, 5
2.13.1	Methodology/Validation	R	1
2.13.2	Confirmation of Identity	R	1, 6
2.13.3	Batch Data	R	1
2.13.4	Impurities of Toxicological Concern	CR	1
2.14	**Chemical and Physical Properties**		
2.14.1	Colour	R	1
2.14.2	Physical State	R	1
2.14.3	Odour	R	1
2.14.4	Melting Point / Melting Range	R	1
2.14.5	Boiling Point / Boiling Range	R	1
2.14.6	Density or Specific Gravity	R	1
2.14.7	Water Solubility (mg/L)	R	1
2.14.8	Solvent Solubility (mg/L)	R	1
2.14.9	Vapour Pressure	R	1
2.14.10	Dissociation Constant	R	1
2.14.11	Octanol/Water Partition Coefficient	R	1
2.14.12	UV/Visible Absorption Spectra	R	1

Data Code (DACO)	Information Requirement	Required	Test Notes
2.14.13	Stability (Temperature, Metals)	R	1
2.14.14	Storage Stability Data	CR	1
2.15	Sample(s) of Analytical Standards and Residue of Concern	R	1
2.16	Other Studies/Data/Reports	CR	1

1. Information must be provided in accordance with Regulatory Directive DIR98-04, *Chemistry Requirements for the Registration of a Technical Grade Active Ingredient or an Integrated System Product.*
2. Not required if the technical material meets Food Chemicals Codex specifications.
3. For plant extracts and essential oils, a method(s) is required to determine the composition of the product. Major and representative components in each extract/oil must be determined and quantitated. Literature methods are acceptable.
4. For food grade products, a certificate from the supplier that the active ingredient is food grade quality or results of the tests as specified in the Food Chemicals Codex must be provided.
5. For all other categories of products, a decision will be made on a case-by-case basis.
6. For the food grade products, the active ingredient must be identified using the methods outlined in the Food Chemicals Codex.

Table 2 Chemistry Information Requirements for Low-Risk End-Use Products

Data Code	Title	Information Required	Test Notes
0	**Index**	R	
1	**Label**	R	
3	**Chemistry Requirements for the Registration of Manufacturing Concentrates and End-Use Products Formulated from Registered Technical Grade of Active Ingredients**		
3.1	**Product Identification**		
3.1.1	Applicant's Name and Office Address	R	1
3.1.2	Formulating Plant's Name and Address	R	1
3.1.3	Trade Name	R	1
3.1.4	Other Names	R	1
3.2	**Formulation Process**		
3.2.1	Description of Starting Materials	R	1
3.2.2	Description of the Formulation Process	R	1
3.2.3	Discussion of the Formation of Impurities of Toxicological Concern	CR	1
3.3	**Specifications**		
3.3.1	Establishing Certified Limits	R	1
3.3.2	Control Product Specification Form	R	1
3.4	**Product Analysis**		
3.4.1	Enforcement Analytical Method	R	1, 2, 3, 4
3.4.2	Impurities of Toxicological Concern	CR	1
3.5	**Chemical and Physical Properties**		
3.5.1	Colour	CR	1
3.5.2	Physical State	R	1
3.5.3	Odour	CR	1

Data Code	Title	Information Required	Test Notes
3.5.4	Formulation Type	R	
3.5.5	Container Material and Description	R	
3.5.6	Density or Specific Gravity	R	1
3.5.7	pH	R	1
3.5.8	Oxidizing or Reducing Action (Chemical Incompatibility)	R	1
3.5.9	Viscosity	R	1
3.5.10	Storage Stability Data	R	1
3.5.11	Flammability	R	1
3.5.12	Explodability	R	1
3.5.13	Miscibility	R	1
3.5.14	Corrosion Characteristics	R	1
3.5.15	Dielectric Breakdown Voltage	R	1
3.6	Sample(s)	NR	
3.7	Other Studies/Data/Reports	CR	1

1. Information must be provided in accordance with DIR98-03, *Chemistry Requirements for the Registration of a Manufacturing Concentrate or an End-Use Product Formulated from Registered Technical Grade of Active Ingredients or Integrated System Products*.
2. A method(s) is required to determine the guarantee content for each active ingredient. Literature methods are acceptable.
3. For plant extracts and essential oils, a method(s) is required to determine the guarantee content (major and representative components in each extract/oil). Literature methods are acceptable.
4. For all other categories, a decision will be made on a case-by-case basis.

Table 3 Toxicology Information Requirements

Data Code (DACO)		USEPA Guideline Number	Information Requirement	Use Patterns		Test Substance		Test Notes
TGAI/ ISP	EP			Food	Non-Food			
Use Patterns (1) Food use patterns, in general, include products classified under the following general uses: terrestrial food crop use; terrestrial feed crop use; aquatic food crop use; greenhouse food crop use. (2) Non-food use patterns include products classified under the general use patterns of terrestrial non-food crop use; aquatic non-food domestic use; aquatic non-food outdoor use; aquatic non-food industrial use; greenhouse non-food crop use; forestry use; domestic outdoor use; domestic indoor use; indoor food use; indoor non-food use; indoor medical use. *Key*. R = Required; CR = Conditionally required; NR = Not required; TGAI = Technical grade of active ingredient; ISP = Integrated system product; EP = End-use product								
Tier I								
Acute Studies								
4.2.1	4.6.1	870.11	Acute Oral	R	R	TGAI/ISP	EP	1, 5
4.2.2	4.6.2	870.12	Acute Dermal	R	R	TGAI/ISP	EP	2, 5, 6
4.2.3	4.6.3	870.13	Acute Inhalation	R	R	TGAI/ISP	EP	1, 7

Data Code (DACO)		USEPA Guideline Number	Information Requirement	Use Patterns		Test Substance		Test Notes
TGAI/ ISP	EP			Food	Non-Food			
4.2.4	4.6.4	870.24	Primary Eye Irritation	R	R	TGAI/ISP	EP	3, 6
4.2.5	4.6.5	870.25	Primary Dermal Irritation	R	R	TGAI/ISP	EP	3, 5, 6
4.2.6	4.6.6	870.26	Dermal Sensitization	R	R	TGAI/ISP	EP	4, 6, 8
4.2.9	4.6.8	None	Other Acute Studies	CR	CR	TGAI/ISP	EP	9
Short-term Studies								
4.3.1	4.7.1	870.31	Short-term Oral (90 day rodent)	R	CR	TGAI/ISP	EP	1, 11, 10, 12
4.3.2	4.7.3	870.315	Short-term Oral (90 day and/or 12 month dog)	CR	CR	TGAI/ISP	EP	10, 12, 13, 14
4.3.4	4.7.3	870.325	Short-term Dermal (90 day rodent)	CR	CR	TGAI/ISP	EP	1, 12, 16
4.3.6	4.7.6	870.3465	Short-term Inhalation (90 day rodent)	CR	CR	TGAI/ISP	EP	1, 12, 17
4.3.8	4.7.7	None	Other Short-term Studies	CR	CR	TGAI/ISP	EP	12, 15
Special Studies								
4.5.2	NR	870.37	Prenatal Developmental Toxicity (rodent)	R	CR	TGAI/ISP	NR	1, 22, 25, 26
4.5.4	NR	870.51	Genotoxicity: Bacterial Reverse Mutation Assay	R	CR	TGAI/ISP	NR	28
4.5.5	NR	870.53	Genotoxicity: In vitro Mammalian Cell Assay	R	CR	TGAI/ISP	NR	27, 28
4.8	4.8	None	Other Studies/Data/ Reports	CR	CR	TGAI/ISP	EP	9
Tier II								
Mutagenicity Testing (In vivo cytogenetics)								
4.5.7	NR	870.5385	Mammalian Bone Marrow Chromosomal Aberration	CR	CR	TGAI/ISP	NR	29
		870.5395	Mammalian Erythrocyte Micronucleus	CR	CR	TGAI/ISP	NR	29

Data Code (DACO)		USEPA Guideline Number	Information Requirement	Use Patterns		Test Substance		Test Notes
TGAI/ ISP	EP			Food	Non-Food			
Developmental Toxicity								
4.5.3	NR	870.37	Prenatal Developmental Toxicity (non-rodent)	CR	CR	TGAI/ISP	NR	3, 22, 25, 26
Special Studies								
4.3.8	NR	880.355	Immunotoxicity	CR	CR	TGAI/ISP	NR	29, 30
Tier III								
Long-term Studies/Special Studies								
4.4.1	NR	870.41	Chronic Oral (rodent and non-rodent)	CR	CR	TGAI/ISP	NR	1, 18, 19, 32
4.4.2	NR	870.42	Carcinogenicity (rodent species 1)	CR	CR	TGAI/ISP	NR	1, 18, 19, 33
4.4.3	NR	870.42	Carcinogenicity (rodent species 2)	CR	CR	TGAI/ISP	NR	18, 20, 21, 33
4.4.5	NR	880.38	Immune Response	CR	CR	TGAI/ISP	NR	31
Special Studies								
4.5.1	NR	870.38	Reproduction and Fertility Effects	CR	CR	TGAI/ISP	NR	1, 18, 23, 24
4.5.7	NR	870.538	Mammalian Spermatogonial Chromosome Aberration Test	CR	CR	TGAI/ISP	NR	34
NR	4.9	870.72	Safety to Treated Animals	CR	CR	NR	EP	35

1. The preferred species is the rat.
2. The preferred species is the rat or the rabbit.
3. The preferred species is the rabbit.
4. The preferred species is the guinea pig.
5. Not required if the test substance is a gas or highly volatile liquid.
6. Not required if the test substance is corrosive to the skin or has a pH lower than 2 or greater than 11.5.
7. Required if the test substance consists of or under conditions of use will result in a respirable material, e.g. gas, vapour, aerosol or particulate.
8. Required if repeated contact with human skin is likely to occur under conditions of use. Diluted EP testing may be required if the end-use product is diluted under conditions of use.
9. Other available studies that elaborate on the toxicity profile of a test substance.
10. Required for non-food uses that are likely to result in repeated oral exposure to humans.
11. The incorporation of a post-treatment recovery phase should be considered.
12. Depending on the use pattern, this may be required if any component of the end-use product may increase absorption of the active ingredient(s) or increase the toxic or pharmacological effects.
13. May be required when the product is to be used on food or likely come in contact with food.

14. Consideration of a 90-day study in lieu of a 12-month study will be given if this species has demonstrated to be the least sensitive laboratory animal in the 90-day study and there is no evidence for the potential of cumulative or delayed toxicity. Consideration will also be given if the results of the 90-day study and structure-activity relationships of the test substance elicits no specific effects on target organ toxicity when fed at dietary levels of 1–5 % of the total diet composition.

15. This may include other available studies of shorter duration such as range-finding studies that elaborate on the toxicity profile of the test substance.

16. Required to support uses involving purposeful application to the human skin or that would result in comparable prolonged exposure to the product (e.g. insect repellents) and if any of the following criteria are met:

    i) Data from a 90-day oral study are not required.

    ii) The active ingredient is known or expected to be metabolized differently by the dermal route of exposure than by the oral route and the metabolite is of toxicological concern.

    iii) The use pattern is such that the dermal route would be the primary route of exposure.

17. Required if there is a likelihood of significant levels of repeated inhalation exposure to the pesticide as a gas, vapour, or aerosol.

18. The oral route is recommended when the product is to be used on food or likely to come in contact with food.

19. The minimum study duration for the rat should be 24 months.

20. The preferred species is the mouse.

21. The minimum study duration for the mouse should be 18 months.

22. Required if the use of the product under widespread and commonly recognized practice may reasonably be expected to result in significant exposure to female humans (e.g. occupational exposure or repeated application of insect repellents directly to the skin). Tier II data are required on a different test species from Tier I data when developmental effects are observed in the first study and information on species-to-species extrapolation is needed.

23. Required if there is evidence of:

    a) endocrinological effects from the short-term toxicity studies;

    b) developmental effects in the prenatal developmental toxicity study(ies); or

    c) genotoxicity to mammals based on the results from the mutagenicity tests.

    A second litter per generation should be considered if any effect on routinely evaluated reproductive parameters required elucidation, especially at dose levels below those causing minimal adverse effects in repeated exposure studies in the same species; the observed effects in the first litters were induced postimplantation; or the test substance is known or likely to be bioaccumulative, and when blood and tissue levels had not stabilized or attained plateau levels prior to mating.

24. A combined study that uses the two-generation reproduction study in rodents as a basic protocol for the addition of other endpoints or functional assessments in the immature animal is encouraged.

25. Unless the chemical or physical characteristics of the test substance or the likely pattern of human exposure suggests a more appropriate route of exposure, administration by oral intubation is preferred.

26. Additional routes for testing may be requested if prenatal developmental toxicity is observed after oral dosing.

27. This includes choice of assay using the mouse lymphoma L5178Y cells, thymidine kinase (tk) gene locus, maximizing assay conditions for small colony expression and detection; Chinese hamster ovary (CHO) or Chinese hamster lung fibroblast (V79) cells, hypoxanthine-guanine phosphoribosyl transferase (HGPRT) gene locus; or CHO cell strain AS52, xanthine-guanine phosphoribosyl transferase (XPRT) gene locus.

28. It is required to support non-food uses if either

    i) the use is likely to result in significant human exposure; or

    ii) if the active ingredient (or its metabolites) is structurally related to a known mutagen or belongs to any chemical class of compounds containing a known mutagen.

    Additional mutagenicity tests that may have been performed plus a complete reference list (and a copy of each reference) must also be submitted. Subsequent testing may be required based on the available evidence.

29. Required if results from the Tier I mutagenicity tests are positive. Assays using rodent bone marrow, using either metaphase analysis (aberrations) or a micronucleus assay, are preferred.

30. Required if there are effects on hematology, clinical chemistry, lymphoid organ weights and histopathology are observed in the 90-day studies.

31. Required if adverse effects are observed in the Tier II immunotoxicity study. The protocol for evaluating adverse effects to the immune response should be developed after evaluating the effects noted in the immunotoxicity study.

32. Required if the potential for adverse long-term effects is indicated based on any of the following criteria:

i) The short-term effect level established in the following Tier I studies: 90-day (or 12 month) feeding toxicity study, the 90-day dermal toxicity study or the 90-day inhalation toxicity study.

ii) The pesticide use pattern (e.g. rate, frequency, and site of application).

iii) The frequency and level of repeated human exposure that is expected.

33. Required if the product meets either of the following criteria:

i) The active ingredient (or any of its metabolites, degradation products or impurities) produces a morphologic effect (e.g. hyperplasia or metaplasia) in any organ that potentially could lead to neoplastic change in Tier I short-term studies.

ii) Adverse cellular effects suggesting carcinogenic potential are observed in Tier II immunotoxicity and Tier III immune-response study or in Tier II mammalian mutagenicity assays.

In addition, a 90-day range-finding study in rats and mice is required to determine the dose levels if carcinogenicity studies are required. If the mouse carcinogenicity study is not required, the 90-day mouse short-term study is likewise not required.

34. Required if results from lower-tiered mutation or reproductive studies indicate there is potential for chromosomal aberration to occur.

35. May be required if the product's use will result in domestic animals being exposed through, but not limited to, direct application or consumption of treated feed.

Table 4 Occupational Exposure Information Requirements

Data Code (DACO)		USEPA Guideline Number	Information Requirement	Use Patterns		Test Substance	Test Notes
TGAI/ ISP	EP			Food	Non-food		
Use Patterns (1) Food use patterns, in general, include products classified under the following general uses: terrestrial food crop use; terrestrial feed crop use; aquatic food crop use; greenhouse food crop use. (2) Non-food use patterns include products classified under the general use patterns of terrestrial non-food crop use; aquatic non-food domestic use; aquatic non-food outdoor use; aquatic non-food industrial use; greenhouse non-food crop use; forestry use; domestic outdoor use; domestic indoor use; indoor food use; indoor non-food use; indoor medical use. *Key.* R = Required; CR = Conditionally required; NR = Not required; TGAI = Technical grade of active ingredient; ISP = Integrated system product; EP = End-use product							
Tier I							
NR	5.2	875.17	Use Description Scenario (Application and Postapplication)	R	R	EP	1
Tier II							
NR	5.3	None	Pesticide Handlers Exposure Database (PHED) Assessment	CR	CR	EP	2, 3
NR	5.4	875.1100 875.1200 875.1300 875.1400 875.1500	Mixer/Loader/Applicator - Passive Dosimetry	CR	CR	EP	2, 4

Data Code (DACO)		USEPA Guideline Number	Information Requirement	Use Patterns		Test Substance	Test Notes
TGAI/ ISP	EP			Food	Non-food		
NR	5.5	875.1100 875.1200 875.1300 875.1400 875.1500 875.2600	Mixer/Loader/Applicator - Biological Monitoring	CR	CR	EP	2, 5
NR	5.6	860.1200 875.2400 875.2500 875.2600	Postapplication - Passive Dosimetry	CR	CR	EP	2, 4
NR	5.7	860.1200 875.2400 875.2500 875.2600	Postapplication - Biological Monitoring	CR	CR	EP	2, 5
NR	5.8	870.76	Dermal Absorption Study	CR	CR	EP	2, 6, 7
NR	5.9	860.1200 875.2100 875.2200 875.2400 875.2500 875.2600	Dislodgeable Residues (Foliar, Soil and Surface)	CR	CR	EP	2, 8
NR	5.1	875.2400 875.2500 875.2600	Ambient Air Samples	CR	CR	EP	2, 9
NR	5.11	875.1100 875.1200 875.1300 875.1400 875.1500	Gloves/Clothing Penetration Data	CR	CR	EP	2
NR	5.12	None	Epidemiology	CR	CR	EP	2
NR	5.13	None	Package Integrity Study	CR	CR	EP	2

1. Information that fully describes the proposed use of the product(s) and the human activity associated with its use should be submitted, if applicable.

   Mixer/Loader/Applicator —site of application, size of crop and area of crop that can be treated in a work day, description of typical application rates, number of applications per season, frequency of applications, when the product is to be applied relative to standard cultivation practices, crop height at application, method of application, individuals involved, mixing/loading method, clean-up and repair activities, and personal protective equipment and clothing.

   Postapplication—method of crop cultivation; restricted-entry intervals; re-entry activities; timing, frequency, and duration of the re-entry activities; description of the re-entry workers; principle sources of exposure; and personal protective equipment and clothing.

2. These data are required when any toxicology data in Table 3 indicate the biochemical pesticide may pose a potential hazard to the applicator/user. It is recommended that the Agency be consulted prior to study initiation to determine what studies are appropriate based on the nature of the adverse effects seen in the toxicology studies and the available exposure data. Studies performed to support registration of insect repellents may require modifications to these guidelines.
3. The current version of PHED should be used for assessing the exposure.
4. Passive dosimetry studies conducted with surrogate compounds may be acceptable if an acceptable rationale is submitted with the study.
5. Surrogate data may be acceptable if the toxicokinetics are well understood for the purposes of converting internal to external dose.
6. In vivo studies are usually conducted on rodents.
7. In vitro studies should be performed using viable skin and a flow-through apparatus.
8. Media of interest include foliage, indoor surfaces such as carpets, fur or companion animals, soil, etc.
9. Breathing zone samples are preferred.

Table 5 Food Residue Information Requirements

Data Code (DACO)		USEPA Guideline Number	Information Requirement	Use Patterns		Test Substance		Test Notes
TGAI/ ISP	EP			Food	Feed			
Use patterns. (1) Food use patterns, in general, include products classified under the following general uses: terrestrial food crop use; terrestrial feed crop use; aquatic food crop use; greenhouse food crop use. *Key.* R = Required; CR = Conditionally required; NR = Not required; TGAI = Technical grade of active ingredient; ISP = Integrated system product; EP = End-use product								
Metabolism/Toxicokinetic Studies (Nature of Residue)								
6.2	6.2	860.1300 860.1480	Livestock	CR	CR	TGAI/ISP	EP	1, 6, 7, 9
6.3	6.3	860.1300 860.1480	Plants	CR	CR	TGAI/ISP	EP	1, 4, 5
6.4	6.4	860.1300 860.1400 860.1480	Other Studies/Data/ Reports	CR	CR	TGAI/ISP	EP	1, 4, 5, 6, 7, 9
Analytical Methodology								
NR	7.2.1	860.1300 860.1340 860.1360	Supervised Residue Trial Analytical Methodology	CR	CR	NR	EP	1, 4, 5, 6, 7, 8, 9, 10
NR	7.2.2	830.1800 860.1300 860.1340 860.1360	Enforcement Analytical Methodology	CR	CR	NR	EP	8
NR	7.2.3	860.1300 860.1340 860.1360	Inter-laboratory Analytical Methodology	CR	CR	NR	EP	9, 10

Data Code (DACO)		USEPA Guideline Number	Information Requirement	Use Patterns		Test Substance		Test Notes
TGAI/ ISP	EP			Food	Feed			
NR	7.2.4	860.1300 860.1340 860.1360	Multi-residue Analytical Methodology Evaluation	CR	CR	NR	EP	9, 10
NR	7.2.5	860.1300 860.1340 860.1360	Storage Stability of Working Solutions in Analytical Methodology	CR	CR	NR	EP	—
NR	7.3	860.1380 860.1850	Freezer Storage Stability Tests	CR	CR	NR	EP	2
Crop Residue Data								
NR	7.4.1	860.15	Supervised Residue Trial Study	CR	CR	NR	EP	1, 3, 4
NR	7.4.2	860.15	Residue Decline Study	CR	CR	NR	EP	1, 3, 4
NR	7.4.3	860.15	Confined Crop Rotation	CR	CR	NR	EP	1, 3, 4
NR	7.4.4	860.1200 860.1900	Field Crop Rotation Trial Study	CR	CR	NR	EP	1, 3, 4
NR	7.4.5	860.1520 860.1540	Processed Food/Feed	CR	CR	NR	EP	1, 9, 15, 16
NR	7.4.6	860.15	Residue Data for Crops Used as Livestock Feed (if needed for forage crops)	CR	CR	NR	EP	1, 3, 4
NR	7.5	860.1300 860.1480	Livestock, Poultry, Egg and Milk Residue Data (from feeding of treated crops)	CR	CR	NR	EP	1, 6, 7, 9
NR	7.6	860.1300 860.1480	Livestock, Poultry, Egg and Milk Residue Data (external application)	CR	CR	NR	EP	1, 6, 7, 9
NR	7.7	860.15	Tobacco Residue Data	CR	CR	NR	EP	—
NR	7.8	860.1100 860.1300 860.1400 860.1480 860.1550 860.1560 860.1650 860.1850	Other Studies/Data/ Reports	CR	CR	NR	EP	1, 4, 5, 6, 7, 9, 11, 12, 13, 14 17

1. Residue chemistry data requirements apply to biochemical pesticide products when Tier II or Tier III toxicology data are required, as specified for biochemical pesticides in Table 3.

2. Storage stability data will be required in conjunction with most magnitude of residue studies, e.g. crop field trials, processing studies, livestock feeding studies, and for primary standards, stock solutions and working solutions of standards. The Agency will make the following exception: unless a pesticide or residue of concern is otherwise known to be volatile or labile, storage stability data will not be needed for samples stored frozen for less than 30 days.
3. Required information includes crops to be treated, rate of application, number and timing of applications, preharvest intervals, and relevant restrictions.
4. Residue data for outdoor residential uses are required if home gardens are to be treated and the home garden use pattern is different from use patterns where tolerances/maximum residue limits have been established.
5. Required for indoor uses where the pesticide is applied directly to food, in order to determine metabolites and/or degradation products.
6. Data on metabolism in livestock are required when residues occur on a livestock feed or if the pesticide is to be applied directly to livestock. If results from the plant metabolism study show differing metabolites in plants from those found in animals, an additional livestock metabolism study involving dosing with the plant metabolite(s) may also be required.
7. Livestock feeding studies are required whenever a pesticide residue is present in livestock feed or when direct application to livestock uses occurs.
8. A residue method suitable for enforcement of tolerances/maximum residue limits is required whenever a numeric tolerance/maximum residue is proposed.
9. Required for indoor uses if the indoor use could result in pesticide residues in or on food or feed.
10. Data are required to determine whether multiresidue methodology would detect and identify the pesticides and any metabolites.
11. Data on residues in potable water are required whenever a pesticide is to be applied directly to water, unless it can be determined that the treated water would not be used (eventually) for drinking purposes, by humans or animals.
12. Data on residues in fish are required whenever a pesticide is to be applied directly to water inhabited, or that will be inhabited, by fish that may be caught or harvested for human consumption.
13. Data on residues in irrigated crops are required when a pesticide is to be applied directly to water that could be used for irrigation or to irrigation facilities such as irrigation ditches.
14. Data on residues in food/feed in food handling establishments are required whenever a pesticide is to be used in food/feed handling establishments.
15. Data on the nature and level of residue in processed food/feed are required when detectable residues could concentrate on processing.
16. Anticipated residue data are required when the assumption of tolerance level/maximum residue limit residues would result in predicted exposure at an unsafe level of exposure. Data on the level or residue in food as consumed would be used to obtain a more precise estimate of potential dietary exposure.
17. The proposed tolerance/maximum residue limit must reflect the maximum residue likely to occur in crops in meat, milk, poultry, or eggs.

Table 6 Environmental Chemistry and Fate and Environmental Toxicology Information Requirements

PMRA Data Code (DACO)	USEPA Guideline Number	Information Requirement	Use Patterns						Test Substance	Test Notes
			Terrestrial Food/Feed, Non-Food	Aquatic Food, Non-Food	Greenhouse Food, Non-Food	Forestry, Residential Outdoor	Indoor Food, Non-Food	Seed Treatment Food/Feed, Non-Food		
Key. R = Required; CR = Conditionally required; NR = Not required; TGAI = Technical grade of active ingredient; ISP = Integrated system product; EP = End-use product										
Tier I										
9.1		Summary of Environmental Toxicology	R	R	R	R	R	R	TGAI/EP	
Avian Testing										
9.6.2.1 9.6.2.2 9.6.2.3	850.2100	Avian Acute Oral Toxicity	R	R	CR	R	CR	R	TGAI/EP	1, 2, 3, 4
9.6.2.4 9.6.2.5 9.6.2.6	850.2200	Avian Dietary Toxicity	R	R	CR	R	CR	R	TGAI/EP	1, 2, 3, 4
Aquatic Organism Testing										
9.5.2.1 9.5.2.2 9.5.2.3	850.1075	Fish Acute Toxicity, Freshwater	R	R	CR	R	CR	CR	TGAI/EP	1, 2, 3, 4, 5
9.3.2	850.1010	Aquatic Invertebrate Acute Toxicity, Freshwater	R	R	CR	R	CR	CR	TGAI/EP	1, 2, 3, 4, 5
Non-Target Plant Testing										
9.8.4	850.4100	Terrestrial Plant Toxicity, Seedling Emergence, Tier I	R	R	NR	R	NR	NR	TGAI/EP	6
	850.4150	Terrestrial Plant Toxicity, Vegetative Vigour, Tier I	R	R	NR	R	NR	NR	TGAI/EP	6

PMRA Data Code (DACO)	USEPA Guideline Number	Information Requirement	Use Patterns: Terrestrial Food/Feed, Non-Food	Aquatic Food, Non-Food	Greenhouse Food, Non-Food	Forestry, Residential Outdoor	Indoor Food, Non-Food	Seed Treatment Food/Feed, Non-Food	Test Substance	Test Notes
Arthropod/Insect Testing										
9.2.4.1 9.2.4.2 9.2.4.3 9.2.5 9.2.6 9.2.7	880.435	Non-Target Arthropod/Insect Testing	R	R	R	R	NR	NR	TGAI/EP	1, 7
Tier II										
Environmental Fate Testing										
8.1		Summary of Environmental Chemistry and Fate	CR	CR	CR	CR	CR	CR	TGAI/EP	8
8.2.4.2	163-1 (835.1230)	Sediment and Soil Adsorption/Desorption for Parent and Transformation Products	CR	CR	CR	CR	NR	CR	TGAI	8
8.2.4.3	163-1 (835.1240)	Soil Column Leaching	CR	CR	CR	CR	NR	CR	TGAI	8
8.2.4.5	163-2 (835.1410)	Laboratory Volatilization from Soil	CR	NR	CR	CR	NR	NR	EP	8
8.2.3.1	161-1 (835.2120)	Hydrolysis	CR	CR	CR	CR	NR	CR	TGAI	8
8.2.3.4.4	161-1 (835.4100)	Aerobic Soil Biotransformation	CR	NR	CR	CR	NR	CR	TGAI	8
8.2.3.3.2	161-2 (835.2240)	Phototransformation in Water	CR	CR	CR	CR	NR	CR	TGAI	8
8.2.3.3.1	161-3 (835.2410)	Phototransformation on Soil	CR	NR	CR	CR	NR	CR	TGAI	8
8.2.3.4.4	162-2 (835.4200)	Anaerobic Soil Biotransformation	CR	NR	NR	NR	NR	NR	TGAI	8

PMRA Data Code (DACO)	USEPA Guideline Number	Information Requirement	Use Patterns						Test Substance	Test Notes
			Terrestrial Food/Feed, Non-Food	Aquatic Food, Non-Food	Greenhouse Food, Non-Food	Forestry, Residential Outdoor	Indoor Food, Non-Food	Seed Treatment Food/Feed, Non-Food		
8.2.3.5.4	162-4 (835.4300)	Aerobic Aquatic Biotransformation	CR	CR	CR	CR	NR	CR	TGAI	8
8.2.3.5.6	162-3 (835.4400)	Anaerobic Aquatic Biotransformation	CR	CR	NR	NR	NR	CR	TGAI	8
8.2.4.6	880.4425	Special Studies: Dispenser—Water Leaching (leaching by water from dispenser)	CR	NR	CR	CR	NR	NR	EP	8
Non-Target Plants										
9.8.4	850.4225	Seedling Emergence, Tier II	CR	CR	NR	CR	NR	NR	TGAI/EP	6, 9
	850.4250	Vegetative Vigour, Tier II	CR	CR	NR	CR	NR	NR	TGAI/EP	6, 9
9.8.2	850.54	Fresh Water Algae	CR	CR	NR	CR	NR	NR	TGAI/EP	1, 10
9.8.5	850.44	Aquatic Vascular Plants	CR	CR	NR	CR	NR	NR	TGAI/EP	1, 10
Tier III										
Aquatic Fauna Chronic, Life Cycle, and Field Studies										
9.3.3 9.5.3.1 9.5.3.2	850.13 850.14 850.15	Freshwater Fish/ Invertebrate Testing	CR	CR	NR	CR	NR	CR	TGAI	11
9.4.4 9.4.2 9.4.2 9.4.3 9.4.5 9.5.3.1 9.5.3.2 9.8.3	850.1025 850.1035 850.1045 850.1055 850.135 850.14 850.15	Marine/Estuarine Fish/ Invertebrate Animal Testing and Marine/Estuarine Algae Testing	CR	CR	NR	CR	NR	CR	TGAI	11
9.3.6 9.4.7 9.5.5	850.195	Aquatic Field Fish/ Invertebrate Testing	CR	CR	NR	CR	NR	CR	EP	12

PMRA Data Code (DACO)	USEPA Guideline Number	Information Requirement	Use Patterns						Test Substance	Test Notes
			Terrestrial Food/Feed, Non-Food	Aquatic Food, Non-Food	Greenhouse Food, Non-Food	Forestry, Residential Outdoor	Indoor Food, Non-Food	Seed Treatment Food/Feed, Non-Food		
Terrestrial Wildlife										
9.6.3.1 9.6.3.2 9.6.3.3	850.2300	Avian Reproduction	CR	CR	NR	CR	NR	CR	TGAI	13
9.7.1	850.24	Wild mammal toxicity	CR	CR	NR	CR	NR	CR	TGAI	13
9.6.5 9.7.2	850.2500	Terrestrial field testing	CR	CR	NR	CR	NR	CR	EP	12
Beneficial Insects										
9.2.9	850.3040	Field Testing for Non-Target Insects (pollinators and beneficial arthropods)	CR	CR	NR	CR	NR	CR	EP	14
Non-Target Plants										
9.8.4	850.4225 850.4250	Non-Target Plants	CR	CR	NR	CR	NR	NR	TGAI, EP	15
9.8.7	850.4300 850.445									

Information requirements may be addressed by submitting a scientifically valid waiver request, publically available information, studies performed on the active ingredients and/or end use products proposed for registration or surrogate information (e.g. on a structurally similar test substance). A rationale should be provided supporting the use of surrogate information.

Test notes. The following test notes are applicable to the information requirements for non-target organisms and environmental fate as referenced in the last column of the table.

1. Required for the end-use product when the end-use formulation may contain other ingredients that may be toxic to non-target organisms or for products that would be available to avian wildlife, (e.g. granular product, treated seed).
2. Tests for pesticides intended solely for indoor application would be required on a case-by-case basis, depending on potential exposure pattern, physical/chemical properties, use volume and other pertinent factors.
3. Not required for any use groups if the pesticide is highly volatile (estimated volatility >5 X 10^{-5} atm m^3/mol).
4. Preferred test species are the bobwhite quail, the mallard duck or the redwing blackbird for avian acute oral toxicity studies; the bobwhite quail or the mallard duck for avian dietary studies; the rainbow trout for acute freshwater fish studies; and *Daphnia magna* for acute freshwater invertebrate studies.
5. Required for seed treatment based on potential exposure pattern (e.g. broadcast application).
6. Testing with the end-use product is preferred. Testing with end-use product is required when the end-use formulation may contain other ingredients that may be phytotoxic.
7. Typically, data on acute toxicity to honeybees satisfies this requirement; however, additional non-target arthropod species may need to be tested to address issues raised by use patterns and potential exposure of important non-target arthropod species, e.g. beneficial predators and parasites.

8. Required on a case-by-case basis when results from Tier I information indicates adverse effects.
9. Tier II data required to support registration of known phytotoxicants, i.e. herbicides, desiccants, defoliants and plant growth regulators, or when phytotoxic effects are determined in Tier I data.
10. Required if Tier I terrestrial plant toxicity data indicated phytotoxicity or if Tier I data indicated aquatic toxicity.
11. Required if information indicates a potential for adverse effects and either persistence in water is observed or chronic exposure can be expected from repeated application. Preferred freshwater test species is *Daphnia magna* or the rainbow trout.
12. The requirement for field studies is determined on a case-by-case basis.
13. Required if information indicates a potential for adverse effects and either persistence in soil or dietary items is observed, or chronic exposure can be expected from repeated application. The preferred avian test species are the bobwhite quail or the mallard duck. Typically, data from the two-generation reproductive toxicity to rats satisfies the requirement for chronic toxicity to small wild mammals.
14. Required when results of Tier I non-target organism information indicates potential adverse effects on non-target insects and results of Tier II tests indicate exposure of non-target insects. Testing with end-use product is required if persistence of residues in or on soil, plants or pollen is observed. Test species depend on use pattern and potential exposure of important non-target insect species.
15. Required if the product is expected to be transported from the site of application by air, soil or water. The extent of movement would be determined by the results of the Tier II environmental fate studies. Test species depend on use pattern and potential exposure of non-target terrestrial and aquatic plants.

Table 7 Value (including efficacy) Information Requirements for End-Use Products

Data Code (DACO)	Information Requirement	Data Required	Conditions
10	**Value**		
10.1	Value summary	**R**	A brief overall summary of the value of the proposed product should be provided.
10.2	**Efficacy studies**		
10.2.1	Mode of action	**R**	The mode of action for the product should be briefly described.
10.2.2	Description of pest problem	**R**	The pest species, biology, and pest/crop interaction should be briefly described.
10.2.3	**Efficacy trials**		
10.2.3.1	Summary	**R**	A brief overall summary of trials and data/rationale submitted to support proposed label claims should be provided.
10.2.3.2	Efficacy: laboratory, growth chamber trials	**CR**	Laboratory data or growth chamber trials may be submitted to support proposed label claims.
10.2.3.3	Efficacy: small-scale trials (field, greenhouse), operational use trials, or published studies	**R**	Either small-scale or operational trials, or published studies are required to support proposed label claims. If published studies are used, rationale for using published studies should be clearly explained.
10.3	**Adverse effects on use site**		
10.3.1	Non-Safety Adverse Effects [e.g.: to crop, sites of application (discolouration, corrosion, etc.)]	**R**	Observations of any adverse effects will be sufficient in most cases.
10.3.3	Damage to Rotational Crops	**CR**	If applicable, depending on the proposed use.
10.4	**Other studies, data, and reports**	**CR**	**If applicable.**

Data requirements for are listed as either "R" for required or "CR" for conditionally required.

Appendix II List of Relevant Publications

Submission Formatting

Regulatory Directive DIR2006-05	*Requirements for Submitting Data Index, Documents and Forms*

Guidelines for General Guidance and Background

Regulatory Directive DIR2005-01	*Guidelines for Developing a Toxicological Database for Chemical Pest Control Products*
Regulatory Directive DIR2001-02	*Guidelines for the Registration of Microbial Pest Control Agents and Products*
Regulatory Proposal PRO2002-02	*Guidelines for the Research and Registration of Pest Control Products Containing Pheromones and Other Semiochemicals*
Regulatory Directive DIR2003-04	Efficacy Guidelines for Plant Protection Products
Regulatory Directive DIR93-17	*Assessment of the Economic Benefits of Pesticides*
Trade Memorandum T-1-255	*Guidelines for Determining Environmental Chemistry and Fate of Pesticides*
Regulatory Proposal PRO96-01	*Management of Submissions Policy*
Regulatory Directive DIR98-01	*Good Laboratory Practice*
Regulatory Directive DIR98-02	*Residue Chemistry Guidelines*
Regulatory Directive DIR98-03	*Chemistry Requirements for the Registration of a Manufacturing Concentrate or an End-Use Product Formulated from Registered Technical Grade of Active Ingredients or Integrated System Products*
Regulatory Directive DIR98-04	*Chemistry Requirements for the Registration of a Technical Grade of Active Ingredient or an Integrated System Product*

Regulatory Directive DIR98-05 *Chemical Pesticides Research Permit Guidelines*

North American Free Trade Agreement (NAFTA) Technical Working Group on Pesticides, *Updated Procedures for Joint Review of Microbials and Semiochemicals*

NOTE: The above documents may be revised in the future. When a revised or final document is issued, the title may be slightly modified and there will be a new reference number. The applicant should contact the PMRA or refer to the PMRA website, accessed through the Health Canada site at www.hc-sc.gc.ca, to determine whether any of the listed references have been superseded by more recent or final versions.